

C. REMARKS

The claims have been amended in order to place the application in better form.

Claims 2-5 and 11 have been cancelled without prejudice and Claim 17 has been added. The fact that Claims 2-5 and 11 have been cancelled without prejudice is not to be construed as an admission by Applicants or Applicants' attorneys that such claims are unpatentable and Applicants reserve the right to prosecute such claims in a continuing application.

Claims 1-3, 5, 6, 9, and 10 stand rejected under 35 U.S.C.102(b) as being anticipated by Hale. This rejection is respectfully traversed.

The present invention, as defined broadly in Claim 1, is directed to a pharmaceutical comprising a therapeutic antibody that binds to a therapeutic target. The antibody is modified with a peptide that inhibits binding of the antibody to the therapeutic target. The modified antibody is effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the therapeutic target. The antibody includes an antibody combining site that binds to the therapeutic target. The peptide is bound to the antibody combining site of the antibody.

Hale discloses the binding of CAMPATH antibodies to mimotopes of the CD52 antigen. The purposes of the binding studies disclosed in Hale were to characterize the CD52 epitope bound by CAMPATH more precisely, and to construct analogues of such epitope that would be useful in assays and for purifying CAMPATH antibodies, as well as for studies of the antibody-antigen binding site.

Although, as the Examiner notes, the TSSPSAD mimotope tested by Hale inhibited binding of the CAMPATH-1H antibody to human lymphocytes, Hale does not

disclose or even remotely suggest to one of ordinary skill in the art that the CAMPATH antibodies, or any other antibody, may be modified with a peptide that reduces binding of the antibody to a therapeutic target, wherein the antibody includes an antibody combining site that binds to the therapeutic target, and the peptide is bound to the antibody combining site.

Hale is directed solely to studying the binding of CAMPATH antibodies to CD52 mimotopes in order to aid in the development of assays, of methods of purifying CAMPATH antibodies, and in studying the antibody-antigen interaction between CAMPATH antibodies and the CD52 antigen or mimotopes thereof. There is nothing in Hale which even remotely suggests to one of ordinary skill in the art that the CAMPATH antibodies may be modified with the mimotopes, or any other compound, in order to inhibit binding of such antibodies to the CD52 antigen. Therefore, for the above reasons and others, Hale does not anticipate Applicants' pharmaceutical as claimed nor does Hale render Applicants' pharmaceutical as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102(b) be reconsidered and withdrawn.

Claims 1 and 2 stand rejected under 35 U.S.C. 102(b) as being anticipated by Waldmann, et al., PCT Application No. W097/31024. This rejection is respectfully traversed.

Waldmann discloses the modification of a therapeutic antibody, whereby as a result of the modification of the antibody, the modified antibody is capable of inducing immunological tolerance to the therapeutic antibody.

In one embodiment, the modified antibody may be a monovalent or divalent fragment, such as an Fab, Fab', or F(ab')<sub>2</sub> fragment or a single chain antibody. In another embodiment the modified antibody includes one or more amino acid substitutions in the CDRs.

The present invention is in marked contrast to Waldmann. In the present invention, the antibody is modified with a peptide that reduces binding of the antibody to the therapeutic target. The peptide is bound to the antibody combining site that binds to the therapeutic target. The modified antibody which is claimed by Applicants is not disclosed or even remotely suggested to one of ordinary skill in the art by Waldmann. Waldmann does not modify an antibody by binding a peptide to the antibody. Instead, Waldmann modifies an antibody by substituting amino acid residues in the antibody, or by employing antibody fragments or single chain antibodies. Therefore, for the above reasons and others, Waldmann does not anticipate Applicants' pharmaceutical as claimed, nor does Waldmann render Applicants' pharmaceutical as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C.102(b) be reconsidered and withdrawn.

The claims stand rejected 35 U.S.C.112, second paragraph, as being indefinite for failing to point out particularly and claim distinctly the subject matter which Applicants regard as the invention. This rejection is respectfully traversed.

The recitation of the term "reduced side effects" in Claim 1 has been deleted, and therefore the Examiner's objections to such term have been obviated.

The Examiner also stated that it is not clear what is contemplated by a therapeutic antibody that produces a therapeutic effect by binding to the therapeutic target, yet is modified such that binding to the therapeutic target is inhibited.

Claim 1 has been amended such that the antibody is defined as an antibody that has been modified such that binding to the therapeutic target is reduced. Therefore one skilled in the art would understand readily that the therapeutic antibody binds to a therapeutic target molecule to produce a therapeutic effect. One skilled in the art also would understand that, when the therapeutic antibody is modified as defined in the claims, the binding of the antibody to the therapeutic target is reduced. Therefore, one skilled in the art would understand that the therapeutic antibody does bind to a therapeutic target, but that the binding of such antibody to such target is reduced when the therapeutic antibody is modified. Therefore, one skilled in the art would understand that a therapeutic effect still is produced. Thus, for the above reasons and others, the claims point out particularly and claim distinctly the subject matter which Applicants regard as the invention. It is therefore respectfully requested that the rejection under 35 U.S.C.112, second paragraph, be reconsidered and withdrawn.

The claims stand rejected 35 U.S.C.112, first paragraph, because the claims contain subject matter which was not described in the specification in such a way as to convey reasonably to one skilled in the relevant art that the inventors, at the time of the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

The Examiner has taken the position that the written description of the present application only conveys reasonably a therapeutic humanized anti-CD52 antibody,

CAMPATH-1H, modified by linking two different mimotope peptides, QTSSPSAD and QTSAAAVD, in which the antibody-mimotope conjugate reduced the immune response and had a therapeutic effect by binding CD52. The Examiner also states that the description of the CAMPATH-1H antibody modified by linking two different peptides, and having the claimed properties is not representative of the entire genus because the genus is highly variable.

Applicants respectfully disagree. The present invention is directed to an antibody which is modified with a peptide which reduces binding of the antibody to a therapeutic target. A multitude of antibodies is known to those skilled in the art. Likewise, peptides also are known to those skilled in the art, and one skilled in the art can modify the antibody with a peptide by techniques that are known to those skilled in the art. In addition, once one skilled in the art modified the antibody with a peptide, one skilled in the art also would be able to determine, by techniques known to those skilled in the art, whether binding of the modified antibody to the therapeutic target had been reduced vis-a-vis the unmodified antibody.

Applicants have shown, as the Examiner admits, that one may modify the CAMPATH-1H antibody with the mimotopes QTSSPSAD or QTSAAAVD. Thus, Applicants have shown that an antibody may be modified with a peptide in accordance with the present invention, and one skilled in the art would understand that other antibodies may be modified with peptides in a similar manner. For the above reasons and others, Applicants have shown that they were in possession of the claimed invention, and it is therefore respectfully requested that the rejection under 35 U.S.C.112, first paragraph, be reconsidered and withdrawn.

The claims stand rejected 35 U.S.C.112, first paragraph, because the specification does not enable any person skilled in the art to make or use the invention commensurate in scope with the claims. This rejection is respectfully traversed.

The Examiner states that the teachings and exemplary guidance in the specification are limited to a humanized anti-CD52 antibody, CAMPATH-1H, linked to a CD52 mimotope, and that there is no guidance or direction of any other therapeutic protein/antibody bound or linked to just any compound, molecule, or peptide that inhibits binding of the protein or antibody to the therapeutic target, reduces side effects and produces a therapeutic effect by binding to the therapeutic target.

As noted hereinabove, Applicants have modified the CAMPATH-1H antibody with two different mimotope peptides. Antibodies which bind to a therapeutic target are known to those skilled in the art. Once Applicants had proven the principle with the CAMPATH-1H antibody, one skilled in the art would know readily how to modify other antibodies with other peptides to reduce the binding of such antibodies to a therapeutic target.

The Examiner, in support of his position, also states that the state of the prior art is such that protein chemistry is probably one of the most unpredictable areas of biotechnology, and cites examples of substitutions of amino acid residues in proteins that affect the activity of such proteins.

Such assertions and Examples provided by the Examiner are nothing more than a "red herring," and have no relevance to whether the claims are enabled.

Applicants modify a known antibody which is known to bind to a known therapeutic target to produce a therapeutic effect. The known antibody is modified by

binding a peptide to the antibody combining site of the antibody in order to reduce the binding of the antibody to the therapeutic target. In addition, as noted hereinabove, the peptide is bound to the antibody combining site of the antibody by means known to those skilled in the art. Once the peptide has been bound to the antibody to form the modified antibody, one then can determine whether binding of the modified antibody to the therapeutic target has been reduced vis-a-vis the unmodified antibody by means known to those skilled in the art. Because Applicants have proven the principle with respect to the CAMPATH-1H antibody bound to two different mimotopes, one skilled in the art would expect reasonably that other antibodies can be modified with other peptides to reduce the binding of such antibodies to their respective therapeutic targets. The Examiner has provided nothing other than sheer speculation in an attempt to show otherwise. It would be contrary to the interests of justice to require Applicants to limit the scope of their protection to an antibody and peptides which are disclosed specifically and enable one to avoid infringement by making modified antibodies outside the scope of Applicants' claims yet within the broad scope of Applicants' inventive discovery. For the above reasons and others, the specification provides an enabling disclosure, and it is therefore respectfully requested that the rejection under 35 U.S.C.112, first paragraph, be reconsidered and withdrawn.

With respect to the obviousness-type double patenting rejection, the Examiner is advised that Application Serial No. 09/979,948 still is pending.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,



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